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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,646	02/18/2004	Jens J. Hyldig-Nielsen	375461-036US	5487
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DECHERT LLP			EXAMINER	
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			ART UNIT	PAPER NUMBER
			1634	
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			06/08/2007	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Advisory Action  
Before the Filing of an Appeal Brief**

Application No.

10/782,646

Applicant(s)

HYLDIG-NIELSEN ET AL.

Examiner

Katherine Salmon

Art Unit

1634

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 24 May 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires \_\_\_\_\_ months from the mailing date of the final rejection.  
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**NOTICE OF APPEAL**

2. ☒ The Notice of Appeal was filed on 24 May 2007. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

**AMENDMENTS**

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
(a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);  
(b) ☐ They raise the issue of new matter (see NOTE below);  
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: See Continuation Sheet. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
5. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.  
6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
The status of the claim(s) is (or will be) as follows:  
Claim(s) allowed: \_\_\_\_\_.  
Claim(s) objected to: \_\_\_\_\_.  
Claim(s) rejected: 1-49.  
Claim(s) withdrawn from consideration: \_\_\_\_\_.

**AFFIDAVIT OR OTHER EVIDENCE**

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

**REQUEST FOR RECONSIDERATION/OTHER**

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:  
See Continuation Sheet.  
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_.  
13. ☐ Other: \_\_\_\_\_.

/Carla Myers/  
Primary Examiner, Art Unit 1634

Continuation of 3. NOTE: The amendments to the claims are not being entered because the amendments to the claims raise new issues that would require further search and consideration. Whereas the claims previously required only the detection of the signals of the signal probe as a function of temperature, the currently amended claims require the monitoring of turning off the signal of the first probe at a temperature below the melting temperature of the quencher probe and monitoring the turning on of the signal of the first signal probe when the temperature is above the melting temperature of the first quencher probe. Further new Claims 52-56 raise new issues that would require further search and consideration because the currently pending claims do not specifically require the use of a second quencher that is not fluorescent or quencher probes that quench by a non-FRET mechanism. The amendments to the claims recite method steps which raise new issues under 35 USC 102 and 35 USC 103 that would require further search and consideration.

Continuation of 11. does NOT place the application in condition for allowance because: The arguments presented in the reply filed 5/24/2007 have been fully considered, however they have not been found persuasive. (A) The reply asserts that the instant specification makes clear that the invention monitors the signals from the signal fluorophore (donor dye) as opposed to the conventional focus on monitoring signals from the acceptor dye (p. 13 2nd paragraph). The reply asserts that the transference of excitation energy is not used to reflect a positive signal that a target sequence is present in a sample, but rather to silence or quench false-positive signals. (B) The reply asserts that the invention provides a method for detecting target sequences with higher specificity because the claims require the  $T_m$  of the signal probe to be higher than the  $T_m$  of its corresponding quencher probe (p. 13 last paragraph and p. 14 1st sentence). The reply asserts to clarify this function of temperature with respect to the monitoring of the signal-quencher probe pairs; the claims have been currently amended (p. 14 1st paragraph). (C) The reply asserts that Figure 11 of Wittwer et al. does not show the monitoring of signals from fluorescein as a function of temperature (p. 14 2nd paragraph). The reply asserts that the claims require the monitoring of the turning-on of the signal probe when the temperature is below the  $T_m$  of the signal probe but above the  $T_m$  of the quencher probe and that Wittwer et al. does not distinguish the turning on or turning off of signal within a single pair like the claimed invention (p. 14 2nd paragraph). (D) The reply asserts Wittwer et al. provides a contrary teaching because there is a decrease of fluorescence of the acceptor fluorophore of a FRET pair in response to an increase of temperature (p. 15 1st paragraph). (E) The reply asserts that Wittwer does not teach monitoring the signals from a FRET donor as a function of temperature with respect to the relative  $T_m$  of the donor and acceptor probe pair and therefore does not disclose all the limitations of the claims (p. 15 last paragraph). (F) The reply asserts that because Wittwer does not teach all the limitations of the claims the combinations under 35 USC 103 do not teach the limitations of the independent claims (p. 16-23).

(A) It is noted that the claims as examined in the Final mailed 12/04/2007 were drawn to monitoring the detectable signals of the single probes as a function of temperature. However, as stated in the response to arguments on p. 6, Wittwer et al. measures the overall fluorescence released as a function of temperature by measuring the fluorescence of the FRET pair. Wittwer et al. measures the energy of both Cy5 and fluorescein and so therefore Wittwer et al. does measure the signal probe as a function of temperature. The limitations of a transference of excitation energy as a way to silence or quench false-positive signals is not a limitation found in the pending claims.

(B) It is noted that Wittwer et al. teaches a signal probe, which has a melting temperature, which is higher than the quencher probe (Column 4, lines 32-35; Column 12, lines 40-45; Column 12 lines 18-20; and Column 12, lines 29-34 of Wittwer et al. and p. 3 of the Final mailed 12/04/2007). However, the argument that the amendment clarifies the function of temperature with respect to the monitoring of the signal quencher probe pairs is not persuasive because the limitations in the amendment are not recited in the instant claims in view of the non-entry of the after-final amendment.

(C) As stated in section A above, Figure 11 of Wittwer et al. is a ratio of the energy of both Cy5 and fluorescein and therefore Wittwer et al. does measure the signal probe as a function of temperature. However the limitations concerning the turning on and off of probes based on temperature has not been considered because the limitations in the amendments are not recited in the instant claims in view of the non-entry of the after-final amendment.

(D) The reply asserts that Wittwer et al. provides contrary teachings because there is a decrease of fluorescence in response to an increase in temperature, however, it is noted that this limitation is not in the pending claims. Limitations in the amendments of the claims have not been considered because the amendments to the claims have not been entered due to further search and consideration required to examine the new limitations.

(E) It is noted that the pending claims do not have a limitation that the function of temperature is monitored relative to the  $T_m$  of the donor and the acceptor probe pair and therefore Wittwer et al. teaches all the limitations which are in the pending claims. The arguments based on limitations in the amendments are not persuasive because they related to limitations that are not recited in the claims in view of the non-entry of the after final amendment.

(F) Wittwer et al. teaches the limitation of the pending claims and therefore the combination of Wittwer et al. with the secondary references teach the limitations of the pending independent claim. It is noted that the amendments to the independent claims have not been entered and have not been considered to determine if the claims are distinct from the teachings of Wittwer et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Examiner  
Art Unit 1634